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CASE REPORT

An atypical case of late-onset systemic lupus erythematosus with systemic lymphadenopathy and severe autoimmune thrombocytopenia/neutropenia mimicking malignant lymphoma

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Abstract Here, we report a rare case of systemic lupus erythematosus (SLE) with conspicuous manifestation of hematological abnormalities. At onset, the 52-year-old male patient showed systemic lymphadenopathy and splenomegaly, severe autoimmune thrombocytopenia, and autoimmune neutropenia. Bone marrow examination and lymph node biopsy excluded the possibility of malignant lymphoma. Based on laboratory findings, he was finally diagnosed with combined autoimmune cytopenia coupled with SLE. Atypical clinical manifestations of SLE prompted us to explore the possibility of autoimmune lymphoproliferative syndrome (ALPS). However, we did not detect an increased number of $CD4^-/CD8^-$, $CD3^+$, $TCR\alpha\beta^+$ double-negative T cells in the circulating blood or dysfunctional T cell apoptosis in the Fas/Fas ligand pathway due to mutations in the *FAS*, *FASLG* or *CASP10* genes. Combined autoimmune cytopenia is a rare clinical entity that in some cases co-occurs with other autoimmune diseases. Given that most SLE patients presenting atypical hematological manifestations at an early stage subsequently exhibit typical systemic manifestations, the present case raises the possibility that initial hematological abnormalities may be signs of unexpected SLE manifestations.

Keywords Systemic lupus erythematosus (SLE) · Severe autoimmune thrombocytopenia (ITP) · Severe autoimmune neutropenia (AIN) · Autoimmune lymphoproliferative syndrome (ALPS) · Systemic lymphadenopathy · Malignant lymphoma

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disorder with a wide range of clinical manifestation [1]. Although hematological abnormalities including anemia, leukocytopenia, lymphopenia, thrombocytopenia and regional lymphadenopathy are common in SLE, it has been recognized that severe thrombocytopenia (platelet counts $\leq$20,000/μL) and severe neutropenia (neutrophil counts <500/μL) are rare manifestations [2, 3]. Noticeably, SLE scarcely shows generalized lymphadenopathy mimicking lymphoma [4]. Therefore, systemic lymphadenopathy accompanied by hepatosplenomegaly or B symptoms is a warning sign of malignant diseases in elderly people [5]. SLE predominantly affects women, with a high incidence during the childbearing age. The onset of SLE over 50-year-old defined as "late-onset SLE" is uncommon, but is sometimes accompanied by insidious diseases [6]. We here report an atypical case of SLE with conspicuous manifestation of hematological abnormalities. At the onset, the 52-year-old male patient showed systemic lymphadenopathy and

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splenomegaly mimicking malignant lymphoma. He simultaneously had complicated severe autoimmune thrombocytopenia (ITP) and autoimmune neutropenia (AIN).

Case presentation

A 52-year-old male with neither significant past medical history nor appreciable family history presented with systemic lymphadenopathy and splenomegaly and showed exaggerated uptake of ^{18}F-fluorodeoxyglucose (FDG) on positron-emission tomography/computed tomography (PET/CT) scan (Fig. 1). The values for SUV max, SUV mean and SUV peak at the left axillary lymph node were 8.8, 5.0 and 5.9, respectively (Fig. 1). As he did not have significant symptoms other than lymphadenopathy, he stopped going to the regular outpatient clinic on his own accord.

Nine months later, he came to our outpatient unit with gum bleeding, night sweat and fever of unknown origin. Blood examination revealed severe thrombocytopenia, neutropenia and polyclonal hyper-γ globulinemia with elevation of circulating soluble interleukin-2 receptor (Table 1). Enhanced CT scan showed systemic lymphadenopathy and splenomegaly. As we initially suspected hematological malignancies, bone marrow examination and left axillary lymph node biopsy were performed. However, lymph node biopsy revealed hyperplastic reactive changes without specific etiologies. Bone marrow examination also did not show specific changes other than slight hyperplasia. Therefore, we suspected that a kind of autoimmunity would be responsible for symptoms. Expectedly, it was revealed that anti-neutrophil antibody, direct antiglobulin test, platelet-associated IgG, anti-platelet antibody, anti-GPIIb/IIIa antibody and anti-human leukocyte antigen autoantibody were positive in circulating blood (Table 1). We therefore tentatively diagnosed him with ITP and AIN. He showed mild anemia without obvious hemolytic changes. We also detected other multiple autoantibodies including anti-nuclear antibody, anti-cardiolipin antibody and anti-SS-A/Ro antibody. During his hospitalization, refractory cheilitis and mono-neuropathy in the right leg emerged. As patient's physical and laboratory findings met the diagnostic criteria for SLE, we finally diagnosed him with SLE. Although there was prolonged liver dysfunction, liver biopsy did not show specific findings except mild chronic hepatitis.

To prevent possible severe hemorrhage, we administered intravenous immunoglobulin (IVIG) at the dose of 400 mg/kg for 5 days. However, the IVIG therapy was not effective (Fig. 2). Severe thrombocytopenia and neutropenia were improved expeditiously by administration of prednisolone (PSL) at the dose of 1 mg/kg. During tapering of PSL, the number of platelets in the circulating blood was decreased by about $2 \times 10^4/\mu L$. We therefore appended eltrombopag as a second-line therapy. As eltrombopag showed excellent effectiveness at the minimal dose of 12.5 mg, the number of platelets in the circulating blood was increased around $10 \times 10^4/\mu L$. Two months later, PET/CT scan revealed significant improvement in the exaggerated uptake of FDG by lymph nodes and spleen. Furthermore, the value of soluble

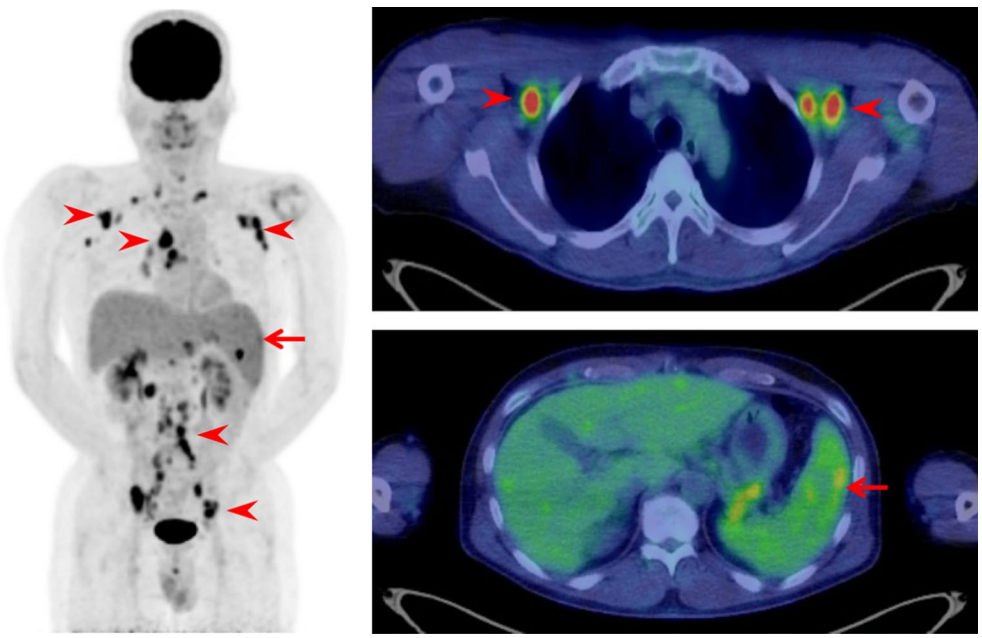

Fig. 1 Images of PET/CT scan in the present case. PET/CT scan showed systemic lymphadenopathy (*black rightward arrowhead*) and splenomegaly (*heavy wide-headed rightward*) exaggerated abnormal uptakes of FDG. The values for SUV max, SUV mean and SUV peak at the left axillary lymph node were 8.8, 5.0 and 5.9, respectively

Table 1 Laboratory findings of the present case on the first admission

CBC		Serum immunology	
WBC	2000/μL	IgG	3443 mg/dL (870–1700)
Baso	2.5%	IgA	360 mg/dL (110–410)
Eo	3.5%	IgM	301 mg/dL (33–190)
Seg	9%	IgG4	85 mg/dL (4–108)
Ly	60%	CRP	1.73 mg/dL
Mono	21%	sIL-2R	3068 U/mL (127–582)
At-Ly	4%	β2MG	3.51 mg/L (0.00–2.00)
RBC	373×10^4/μL	Haptoglobin	169 mg/dL (19–170)
Hb	12.0 g/dL	Type IV collagen	14 ng/mL (≤6)
Hct	35.2%	RF	7 IU/mL (0–14)
MCV	94.4 fl	ANA	(+)
MCH	32.2 pg	Homogeneous	×160 (<×20)
MCHC	34.1%	C3	138 mg/dL (65–135)
Plt	0.9×10^4/μL	C4	8 mg/dL (13–35)
Ret	16‰	CH50	41 U/mL (31–58)
Biochemistry		Anti-dsDNA antibody	7 IU/mL (0–20)
TP	8.3 g/dL	Anti-ssDNA antibody	23 AU/mL (0–40)
Alb	2.9 g/dL	Anti-RNP antibody	0.1 Index (<1.0)
AST	50 IU/L	Anti-Sm antibody	0.5 Index (<1.0)
ALT	47 IU/L	Anti-cardiolipin antibody	16.1 U/mL (<10.0)
LDH	212 IU/L	Anti-SS-A/Ro antibody	29.0 Index (<10.0)
ALP	934 IU/L	Anti-SS-B/La antibody	2.0 Index (<15.0)
γ-GTP	132 IU/L	AMA2 antibody	1.6 Index (<7)
T-bil	0.6 mg/dL	DAT	IgG (3+), C3b, d (−)
BUN	13 mg/dL	PAIgG	883 ng/10^7 cells (≤46)
Cre	0.81 mg/dL	Anti-platelet antibody	(+)
ESR	69 mm/h	Anti-GPIIb/IIIa antibody	(+)
Serum protein fraction		Anti-HLA antibody	(+)
Polyclonal hyper γ globulinemia		Anti-neutrophil antibody	(+)
Hyaluronic acid	300 ng/mL (≤50)	HBs antigen	(−)
Coagulation		Anti-HBs antibody	(−)
PT%	78.5%	Anti-HBc antibody	(−)
APTT	27.9 s	Anti-HCV antibody	(−)
Fib	280 mg/dL	Anti-HIV antibody	(−)
D-Dimer	1.4 μg/mL	Anti-HTLV-1 antibody	(−)
FDP	4 μg/mL	CMV antigenemia	(−)
Urea breath test	(−)	EBV-PCR	2×10^2 copy/mL (<2×10^2)

Peripheral blood testing showed severe thrombocytopenia and neutropenia, polyclonal γ globulinemia, hepatic disorder and multiple autoantibodies (anti-neutrophil antibody, direct antiglobulin test, platelet-associated IgG, anti-platelet antibody, anti-GPIIb/IIIa antibody, anti-human leukocyte antigen autoantibody, anti-nuclear antibody, anti-cardiolipin antibody and anti-SS-A/Ro antibody). In the table each normal value is shown in parenthesis

CBC complete blood count, *WBC* white blood cell, *Baso* basophil, *Eo* eosinophil, *Seg* segmented neutrophil, *Ly* lymphocyte, *Mono* monocyte, *At-Ly* atypical lymphocyte, *RBC* red blood cell, *Hb* hemoglobin, *Hct* hematocrit, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *Plt* platelet, *Ret* reticulocyte, *TP* total protein, *Alb* albumin, *AST* aspartate transaminase, *ALT* alanine transaminase, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *γ-GTP* gamma-glutamyl transpeptidase, *T-bil* total-bilirubin, *BUN* blood urea nitrogen, *Cre* creatinine, *ESR* erythrocyte sedimentation rate, *PT* prothrombin, *APTT* activated partial thromboplastin time, *Fib* fibrinogen, *FDP* fibrin degradation products, *IgG* immunoglobulin G, *IgA* immunoglobulin A, *IgM* immunoglobulin M, *IgG4* immunoglobulin G4, *CRP* C-reactive protein, *sIL-2R* soluble interleukin-2 receptor, *β2MG* beta-2 microglobulin, *RF* rheumatoid factor, *ANA* anti-nuclear antibody, *AMA2* anti-mitochondria M2 antibody, *DAT* direct antiglobulin test, *PAIgG* platelet-associated immunoglobulin G, *HBs antigen* hepatitis B surface antigen, *HBc antibody* hepatitis B core antibody, *HCV antibody* hepatitis C virus antibody, *HIV* human immunodeficiency virus, *HTLV-1* human T cell leukemia virus type 1, *CMV* cytomegalovirus, *EBV* Epstein–Barr virus, *PCR* polymerase chain reaction, (+) positive, (−) negative

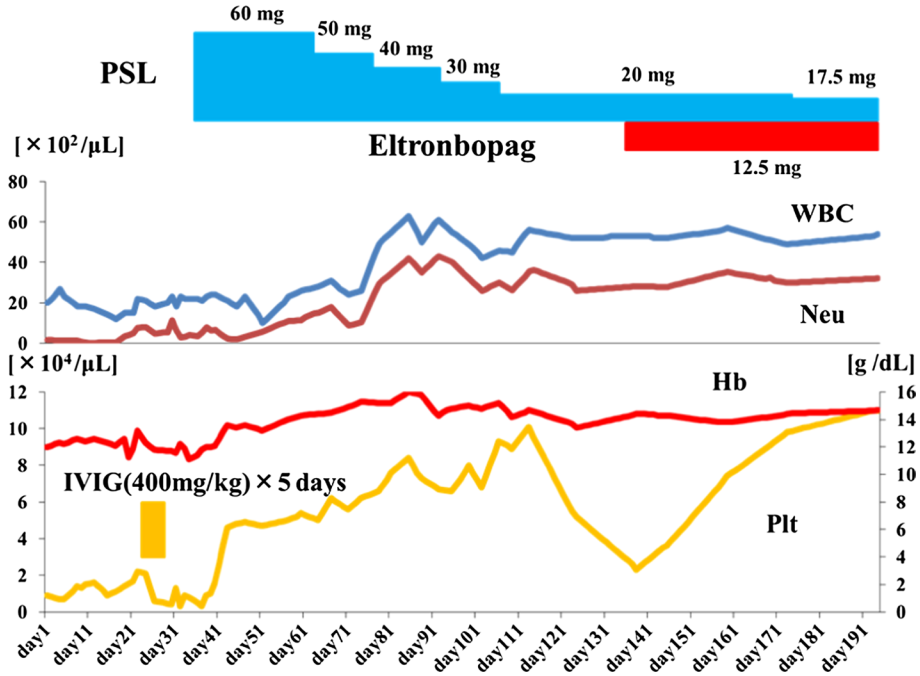

Fig. 2 Clinical course of the present case. As the IVIG therapy was not effective, we administered PSL at the dose of 1 mg/kg. Pancytopenia was improved expeditiously. However, the number of platelet in the circulating blood was decreased by about $2 \times 10^4/\mu L$ during tapering of PSL. After we added eltrombopag at the minimal dose of 12.5 mg, the number of platelets in the circulating blood was successfully increased around $10 \times 10^4/\mu L$. *PSL* prednisolone, *WBC* white blood cell, *Neu* neutrophil, *Hb* hemoglobin, *Plt* platelet, *IVIG* intravenous immunoglobulin

interleukin-2 receptor in the circulating blood decreased to 603 U/mL.

Approximately 2 years after the first admission, he experienced relapse while he was taking PSL 5 mg per day (Table 2). He was again treated with PSL at the dose of 1 mg/kg. His hematological findings improved, and PSL is now being tapered slowly.

Discussion

We experienced an atypical case of late-onset SLE with severe ITP, AIN and marked systemic lymphadenopathy and splenomegaly, closely mimicking malignant lymphoma. At the onset, the patient showed no typical manifestations of SLE including skin lesion, mucous membrane lesions, arthritis or nephritis. In contrast, from the beginning, the patient had systemic lymphadenopathy, night sweat, neutropenic fever and gum bleeding due to severe thrombocytopenia. However, bone marrow examination and lymph node biopsy clearly excluded the possibility of malignant lymphoma. In minor cases, SLE is known to resemble malignant lymphoma or lymphoproliferative disorder [5]. According to Systemic Lupus International Collaboration Clinics (SLICC) criteria [7], he met 2 of 11 clinical criteria (leukopenia and thrombocytopenia) and 4 of 6 immunologic criteria (ANA positivity, antiphospholipid antibody positivity, hypocomplementemia and direct antiglobulin test positivity) for the diagnosis of SLE. Therefore, the patient was finally diagnosed with SLE.

SLE is an autoimmunity-based chronic inflammatory disease that causes a wide variety of organ damages and resultant clinical manifestations [8]. Notably, it is uncommon that the onset of SLE is over 50 years of age (late-onset SLE) [6]. Previous reports on patients with late-onset SLE demonstrated that female to male ratio was low [9] and the frequency of cutaneous, neuropsychiatric manifestations and lupus nephritis was also low, but the frequency of cytopenia was high compared with young patients with SLE [10].

According to the literature, severe ITP coupled with SLE is associated with severe hemorrhagic complications [2]. Although conventional immunosuppressive agents such as corticosteroid and calcineurin inhibitor remain the mainstay against such a situation, thrombopoietin receptor agonist is a novel, promising therapeutic modality [11]. In the present case, the combination therapy of PSL with eltrombopag showed excellent effectiveness.

Of note, the combination of ITP and AIN, as observed in the present case, has been considered as "combined autoimmune cytopenias" [12]. To date, unlike Evans syndrome (ES), there have been only a few reports on combined autoimmune cytopenias. ES is characterized by the co-existence of autoimmune hemolytic anemia (AIHA) and ITP and/or AIN [13]. On the other hand, combined autoimmune cytopenia consists of ITP, AIN and/or AIHA [12]. A recent study reported that approximately half of the adult ES patients have a variety of underlying diseases including collagen diseases, immunodeficiency diseases, lymphomas and lymphoproliferative disorders [14]. Similarly, combined autoimmune cytopenia is often complicated by underlying diseases [12]. As in the present case, the majority of late-onset SLE patients who limitedly exemplified

Table 2 Laboratory findings of the present case on the second admission

CBC		Coagulation	
WBC	3400/μL	PT%	73.0%
Eo	2.0%	APTT	28.7 s
Myelo	(+)	Fib	558 mg/dL
Meta	1.0%	D-Dimer	0.9 μg/mL
Stab	14.0%	FDP	5 μg/mL
Seg	2.0%	Serum immunology	
Ly	53%	IgG	1592 mg/dL (861–1747)
Mono	28%	IgA	326 mg/dL (93–393)
RBC	429 × 10^4/μL	IgM	169 mg/dL (33–183)
Hb	13.8 g/dL	CRP	11.56 mg/dL
Hct	40.1%	sIL-2R	827 U/mL (127–582)
MCV	93.5 fl	Haptoglobin	118 mg/dL (19–170)
MCH	32.2 pg	RF	<5 IU/mL (0–14)
MCHC	34.4%	ANA	(+)
Plt	0.6 × 10^4/μL	Homogeneous	×40 (<×20)
Ret	36.5‰	C3	142 mg/dL (65–135)
Biochemistry		C4	21 mg/dL (13–35)
TP	7.6 g/dL	CH50	59 U/mL (31–58)
Alb	3.7 g/dL	Anti-dsDNA antibody	3 IU/mL (0-12)
AST	63 IU/L	Anti-ssDNA antibody	5 AU/mL (0-25)
ALT	103 IU/L	Anti-cardiolipin antibody	1.1 U/mL (<10.0)
LDH	229 IU/L	Anti-SS-A/Ro antibody	1.3 Index (<10.0)
ALP	636 IU/L	Anti-SS-B/La antibody	0.9 Index (<15.0)
γ-GTP	164 IU/L	DAT	IgG (−), C3b, d (−)
T-Bil	2.9 mg/dL	PAIgG	142 ng/10^7 cells (≤46)
D-Bil	1.1 mg/dL	Anti-platelet antibody	(−)
BUN	16 mg/dL		
Cre	1.01 mg/dL		
ESR	69 mm/h		

His blood test revealed marked severe thrombocytopenia and neutropenia. In the table each normal value is shown in parenthesis

CBC complete blood count, *WBC* white blood cell, *Baso* basophil, *Eo* eosinophil, *Myelo* myelocyte, *Meta* metamyelocyte, *Stab* stab neutrophil, *Seg* segmented neutrophil, *Ly* lymphocyte, *Mono* monocyte, *RBC* red blood cell, *Hb* hemoglobin, *Hct* hematoclit, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *Plt* platelet, *Ret* reticulocyte, *TP* total protein, *Alb* albumin, *AST* aspartate transaminase, *ALT* alanine transaminase, *LDH* lactate dehydrogenase, *ALP* alkaline phosphatase, *γ-GTP* gamma-glutamyl transpeptidase, *T-Bil* total-bilirubin, *D-Bil* direct-bilirubin BUN blood urea nitrogen, *Cre* creatinine, *ESR* erythrocyte sedimentation rate, *PT* prothrombin, *APTT* activated partial thromboplastin time, *Fib* fibrinogen, *FDP* fibrin degradation products, *IgG* immunoglobulin G, *IgA* immunoglobulin A, *IgM* immunoglobulin M, *CRP* C-reactive protein, *sIL-2R* soluble interleukin-2 receptor, *RF* rheumatoid factor, *ANA* anti-nuclear antibody, *DAT* direct antiglobulin test, *PAIgG* platelet-associated immunoglobulin G, (+) positive, (−) negative

atypical hematological manifestations without typical lupus signs are less likely to be diagnosed with SLE. Therefore, it is required to periodically monitor autoantibodies such as ANA and ds-DNA, indicating the disease activity of SLE.

Atypical clinical manifestations of SLE in the present case tempted us to explore the possibility of autoimmune lymphoproliferative syndrome (ALPS) as a plausible differential diagnosis. ALPS is an immune-deficient disease caused by dysfunction of T cell apoptosis in the Fas/Fas ligand pathway due to mutations in the *FAS*, *FASLG* and *CASP10* genes [15]. ALPS is characterized by the presence of chronic, non-malignant, non-infectious lymphadenopathy and/or splenomegaly. In circulating blood from patients with ALPS, $CD4^-/CD8^-$, $CD3^+$ and $TCR\alpha\beta^+$ double-negative T cell (DNT) counts were reported to increase in many cases [15]. Although the onset of ALPS is typically observed in childhood, some cases of ALPS were reported to be diagnosed during adulthood [16]. We therefore investigated the

DNT counts and possible gene mutations via the Internet web site of Primary Immunodeficiency Database in Japan (http://pidj.rcai.riken.jp/). However, increased number of DNT counts as well as gene mutations for *FAS*, *FASLG* and *CASP10* was not detected, and hence the exclusion of ALPS.

In summary, we reported a 52-year-old male SLE patient presenting with severe ITP, AIN and systemic lymphadenopathy without typical manifestations of SLE. The present case raises the alarm of considering the possibility that initial hematological abnormalities may be signs of unexpected SLE manifestation.

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Compliance with ethical standards

All authors follow the compliance with ethical standards.

Conflict of interest All authors declare no conflict of interest.

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